American Journal of Medical Genetics 63:529–536 (1996)

VACTERL Association, Epidemiologic Definition and Delineation

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This study departed from a preconceived definition of VACTERL, including more than one of these six anomalies in the same infant: V (vertebral anomalies), A (anal atresia), C (congenital heart disease), TE (tracheo-esophageal fistula or esophageal atresia), R (reno-urinary anomalies), and L (radial limb defect). Under this definition, 524 infants were ascertained by ECLAMC from almost 3,000,000 births examined from 1967 through 1990.

Observed association rates among VACTERL components as well as between VACTERL and other defects were compared against randomly expected values obtained from 10,084 multiply malformed infants (casuistic method) from the same birth sample.

Conclusions were: 1) Cardiac defects are not a part of VACTERL. 2) Single umbilical artery, ambiguous genitalia, abdominal wall defects, diaphragmatic hernia, and anomalies that are secondary to VACTERL components (intestinal and respiratory anomalies, and oligohydramnios sequence defects) are frequent enough to be considered an "extension" of VACTERL, and cardiac defects should be included in this category. 3) Neural tube defects are negatively associated with VACTERL which could not be explained by selection bias or any other operational artifact. High embryonic lethality or mutually exclusive pathogenetic mechanisms could be suitable explanations. 4) Results were not clear enough to determine whether VACTERL should be defined by at least two or three component defects.

Received for publication June 15, 1995; revision received October 30, 1995.

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KEY WORDS: VACTERL, VATERL, VATER, Associations

INTRODUCTION

The VATER association was originally described by Quan and Smith [1973], as the non-random co-occurrence of five defects, namely, vertebral anomalies (V), anal atresia (A), esophageal atresia and/or tracheo-esophageal fistula (TE), and radial and renal anomalies (R standing for both of them). Thereafter, a number of other defects were added to the originally described set, mainly on clinical grounds. Cardiac and genital anomalies, single umbilical artery, limb anomalies, others than radial, and the caudal regression complex, among others, were included as part of the spectrum [Temtamy and Miller, 1974; Lubinsky, 1980; Smith, 1982]. VACTERL is the acronym most frequently used in the literature, where C stands for cardiovascular anomalies and L for radial or other limb component, leaving R for the renal anomaly [Kaufmann, 1973; Nora and Nora, 1975]. No specific cause has been identified and causal heterogeneity seems to be the most acceptable conclusion [Khoury et al., 1983]. The literature is unclear about a definite delineation and about establishing clear limits to this association [Evans, 1982; Lubinsky, 1986].

Published epidemiological data are limited to only two large series, those of Khoury et al. [1983] and Czeizel and Ludanyi [1984, 1985].

The aims of this study were to determine which defects belong to VACTERL, how many of them should be considered to define this entity, and the existence of either positive or negative associations with other non-VACTERL defects.

MATERIALS AND METHODS

The ECLAMC is a hospital-based malformation monitoring system, which has been operating since 1967 in 12 Latin-American countries. It covers about 150,000 live and stillbirths a year, and records all major and minor malformations diagnosed at birth or before their discharge from the maternity hospital [Castilla and Orioli, 1983].

TABLE I. Number of Cases With One or More of the Six VACTERL Components Observed Among 61,178 Malformed Newborn Infants

Component defects		Single N = 51,094	Multiple N = 10,084	Total N = 61,178
V	Vertebral	35	302	337
A	Anal	350	537	887
C	Cardiac	1,453	1,327	2,780
TE	Tracheo-esophageal	300	291	591
R	Renal	263	537	800
L	Limb (preaxial)	464	270	734

From 1967 through 1990, 2,493,999 births were examined; 61,178 of them (2.45%) had one or more congenital anomalies, 10,084 of which (16.48%) having two or more malformations (Table I). From this set of 10,084 cases, VACTERL cases were defined as having two or more of the following six anomalies, with or without other associated defects: Vertebral anomalies (V), excluding spina bifida aperta; anal atresia (A), including high (rectal atresia) and low (imperforate anus) atresias, with or without fistula; cardiovascular anomalies (C) excluding single umbilical artery; and tracheoesophageal fistula (TE) including esophageal atresia and/or tracheoesophageal fistula, renal anomalies (R), including defects of the urinary system but excluding exstrophy of the bladder, and limb defects (L) including preaxial anomaly (deficiency or polydactyly) of the upper limbs.

While vertebral (V), renal (R), and cardiovascular (C) anomalies are collective categories, including a wide variety of defects at a given anatomical organ, anal atresia (A), tracheoesophageal fistula (TE), and preaxial anomaly of the upper limbs (L) are rather specific defects which anatomical subtypes do not imply recognized dysmorphologic differences. Therefore, the defects included in the three collective VACTERL components (V, C, and R) are specified in Table II.

VACTERL cases were classified as "associated," when other than the above-mentioned six VACTERL defects were also present in the same infant, or "isolated" when they were not. Cases were further subdi-

TABLE II. Number of Cases by Subtype of Three Collective VACTERL Components

Component/subtype	VACTERL-isolated	VACTERL-associated	VACTERL-total
V Vertebral			
Hemivertebrae	15	43	58
Spina bifida occulta	0	1	1
Scoliosis	1	16	17
Generalized anomaly	0	8	8
Lordosis	0	1	1
Other specified anomalies	10	47	57
Total	26	116	142
C Cardiovascular			
Truncus arteriosus	0	5	5
Transposition	1	1	2
Tetralogy	4	4	8
VSD	8	37	45
ASD	6	17	23
Canal AV communis	0	2	2
Anomalous valves	1	2	3
Dextrocardia	3	18	21
Cardiomegaly	0	7	7
Heart hypoplasia	0	2	2
Left heart hypoplasia	0	2	2
Complex defect	1	10	11
PDA	5	15	20
Coarctation of aorta	2	5	7
Hypoplasia of aorta	0	1	1
Pulmonary stenosis	1	1	2
Other subtypes	21	49	70
Total	53	178	231
R Renourinary			
Renal dysplasia	9	67	76
Polycystic kidney[a]	6	55	61
Hydronephrosis	10	39	49
Urethral atresia	2	22	24
Other anomalies	10	48	58
Total	38	231	262

[a] Includes multicystic kidneys.

vided according to the number of VACTERL components present (Table III).

The strength of the association between two given anomalies was initially measured through observed/expected ratios, with expected values obtained by the following three methods. One was the "population" method [Källén and Winberg, 1968] deriving expected values from the whole sample of 61,178 malformed infants within the 2,493,999 examined births. Another one was the "casuistic" approach of Källén [1988], comparing the number of cases with a given diad (defined as a pair of anomalies with or without other associated anomalies) with their number expected by chance association within the total set of 10,084 multiply malformed babies. The third method employed was the "adjusted" method described by Khoury et al. [1990], comparing the number of cases with a given diad with their random expected number derived from the multiply malformed infants having at least one of the defects involved in the diad.

The casuistic approach was preferred because it not only depends on the defects under consideration but also on the extent of clustering among other defects, using the total sample of multiply malformed infants as the denominator. Furthermore, this method reduces the ascertainment bias of a given defect when it is present alone or in association with others. This casuistic approach was applied to evaluate the association among VACTERL component anomalies, as well as between VACTERL and non-VACTERL defects.

Observed/expected differences were tested by the Z test and the limit of significance was set at 5% for the intra-VACTERL, and at 1% for the extra-VACTERL comparisons because of the large number of comparisons made in the latter group. The differences of VACTERL components and diads between cases with two and with three or more components were tested by chi-square, with the limit of significance set at 5%.

In order to facilitate the comparison with other data sets, Table II specifies the different anomalies that were included among the different VACTERL components and Appendix A shows the observed number of cases for each one of the 77 theoretically possible combinations of the six VACTERL components: 15 of 2, 40 of 3, 15 of 4, 6 of 5, and 1 of 6.

RESULTS

A total of 524 cases had more than one of the six VACTERL component anomalies, 103 being classified as isolated, and 421 as associated due to the presence of other non-VACTERL anomalies in the same patient. Among the latter, 53 cases with specific syndromes were identified: trisomy 18 syndrome, 20 cases; trisomy 21 syndrome, 14 cases; trisomy 13 syndrome, 6 cases; Holt Oram syndrome, 6 cases; Meckel syndrome, 3 cases; Ullrich Turner syndrome, 2 cases; 1 case with 1p+; and 1 case with acardioacephalus.

Four hundred sixteen cases (82 isolated and 334 associated) had only two VACTERL components (pairs), while 108 (21 isolated and 87 associated) had three (triplets) or more (quadruplets, quintuplets, and sextuplets). These 524 cases involved 1,186 instances of combination among the six VACTERL component anomalies: 234 combinations in 103 isolated cases and 952 combinations in 421 associated cases (Table III).

When looked at individually, the instances of association between VACTERL components taken two at a time (diads) fit into 15 theoretically possible combinations. Eleven of them showed a significant association (observed/expected ratios with P values lower than 0.001), while the association rates of RL, CL, VC, and AC were not significant. In Table IV, the diads are listed according to their decreasing observed/expected ratios. Even when significance values vary according to the method employed to estimate expected numbers, the ranking of diads by their O/E ratios remain approximately the same, leaving always the following seven diads with the lowest O/E values: AL, CR, CTE, RL, CL, VC, and AC, noteworthy including all the five diads involving cardiac defects (C).

The combinations with the highest association rates were ATE, anal and esophageal atresias; LTE, radial defect and esophageal atresia; VA, vertebral anomaly and anal atresia; VTE, vertebral anomaly and esophageal atresia; and AR, anal atresia and renal anomaly. All five diads involving cardiovascular defects (C)

TABLE III. Number of Combinations Observed Among the Six VACTERL Components, According to the Number of Involved Components in 103 Isolated and 421 Associated VACTERL Cases

	Number of VACTERL components											
	Isolated						Associated					
	2	3	4	5	6	Total	2	3	4	5	6	Total
Cases	82	15	5	1	0	103	334	69	14	3	1	421
Instances[a]												
V	13	8	4	1	0	26	76	27	9	3	1	116
A	38	10	4	1	0	53	137	46	11	3	1	198
C	41	5	3	0	0	49	173	40	7	3	1	224
TE	39	8	3	1	0	51	79	31	12	3	1	126
R	21	7	3	1	0	32	159	44	9	1	1	214
L	12	7	3	1	0	23	44	19	8	2	1	74

[a] V, vertebral anomaly; A, anal atresia; C, cardiac defect; TE, tracheo-esophageal fistula; R, renal anomaly; L, limb (radial) defect.

TABLE IV. Observed and Expected Instances of Association Among VACTERL Components Presented by Decreasing O/E Ratios*

	Observed	Expected	Z	P	O/E
Diads					
ATE	82	15.50	16.89	<0.0001	5.29
TEL	39	7.79	11.18	<0.0001	5.01
VA	73	16.08	14.19	<0.0001	4.54
VTE	34	8.71	8.57	<0.0001	3.90
AR	97	28.60	12.79	<0.0001	3.39
VL	27	8.09	6.65	<0.0001	3.34
VR	43	16.08	6.71	<0.0001	2.67
TER	41	15.50	6.48	<0.0001	2.65
AL	32	14.38	4.65	<0.0001	2.23
CR	131	70.67	7.18	<0.0001	1.85
CTE	66	38.29	4.48	<0.0001	1.72
RL	18	14.38	0.95	0.3421	1.25
CL	42	35.53	1.09	0.2757	1.18
VC	43	39.74	0.52	0.6030	1.08
AC	69	70.67	−0.20	0.8414	0.98
Triads					
VATE	19	0.45			42.22
VTEL	11	0.27			40.74
ATEL	14	0.45			31.11
VAL	13	0.45			28.89
VAR	21	1.11			18.92
ATER	16	1.06			15.09
TERL	9	0.64			14.06
VTER	6	0.64			9.38
VCTE	11	1.31			8.40
CTEL	10	1.36			7.35
VCL	7	1.23			5.69
ARL	6	1.06			5.66
VRL	3	0.64			4.69
ACTE	10	2.27			4.41
VAC	10	2.33			4.29
ACR	21	5.29			3.97
CTER	12	3.18			3.77
ACL	6	2.27			2.64
CRL	8	3.18			2.52
VCR	8	3.31			2.42
Tetrads					
VATEL	8	0.013			615.38
VATER	6	0.031			193.55
VCTEL	5	0.040			125.00
VTERL	2	0.018			111.11
VARL	3	0.031			96.77
VACTE	5	0.068			73.53
ATERL	2	0.031			64.52
VACL	3	0.068			44.12
ACTEL	3	0.068			44.12
CTERL	3	0.095			31.58
ACTER	4	0.158			25.32
VACR	4	0.158			25.32
VCTER	2	0.095			21.05
ACRL	2	0.158			12.66
VCRL	1	0.095			10.53
Pentads					
VATERL	2	0.00095			2105.26
VACTEL	3	0.0020			1500.00
VACTER	2	0.0048			416.67
VCTERL	1	0.0029			344.83
ACTERL	1	0.0048			208.33
VACRL	1	0.0048			208.33
Hexad					
VACTERL	1	0.00014			7142.86

* Statistical analysis not done in triads, tetrads, pentads, and hexads, because of low expected numbers.

fell among the lowest O/E ratios, as well as RL (renal plus radial defects). Because of their low expected numbers, statistical analysis was not done for triads, tetrads, pentads, and hexads, for which only O/E ratios are shown (Table IV).

VACTERL cases with two and with more than two component defects were compared. Cardiac defects were more ($P < 0.05$) and radial limb defects less ($P < 0.01$) frequent in the former than in the latter groups. When taken two at a time, the VTE diad was less ($P < 0.02$), and the CR diad was more ($P < 0.05$) frequent among VACTERL cases with 2 as compared with those with more than 2 component defects (Table V).

The association rates between VACTERL and other non-VACTERL defects are shown in Table VI. Among those associations with more than five expected cases, significant association rates ($P < 0.01$) were found for ambiguous genitalia, prune belly, single umbilical artery, lung hypoplasia, other than esophageal or anal atresia intestinal defects, diaphragmatic hernia, and abdominal wall defects.

Ten non-VACTERL defects were negatively associated with VACTERL ($P < 0.01$): micrognathia, talipes talovalgus, postaxial polydactyly, syndactyly, microcephaly, preauricular tags, angiomas, hip dislocation, spina bifida, and anencephaly. Only the latter two defects are major malformations, both of them being neural tube defects.

Among syndromes, VACTERL was positively associated with trisomy 18 (20 observed/7.95 expected = 2.52; Z = 4.27; $P = 0.0001$), and negatively with Down syn-

TABLE V. Frequency of Each Component and of Each Diad of Components in 416 Cases With 2 and 108 Cases With Three or More Components (Isolated Plus Associated Cases)

	VACTERL ISO + ASO					
	2		3 or more		χ^2	P*
Components	N	%	N	%		
V	89	10.7	53	15.0	3.78	—
A	175	21.0	76	21.5	0.03	—
C	214	25.7	59	16.7	8.85	<0.05
TE	118	14.2	59	16.7	1.04	—
R	180	21.6	66	18.6	1.07	—
L	56	6.7	41	11.6	7.09	<0.01
Total	832	99.99	354	100.1		
Diads						
VA	32	9.3	40	9.6	0.01	—
VC	21	6.1	19	4.5	0.84	—
VTE	8	2.3	26	6.2	6.33	<0.02
VR	19	5.5	24	5.7	0.03	—
VL	9	2.6	18	4.3	1.53	—
AC	37	10.8	32	7.7	2.04	—
ATE	45	13.1	37	8.9	3.15	—
AR	52	15.1	46	11.0	2.51	—
AL	9	2.6	23	5.5	3.69	—
CTE	39	11.3	27	6.5	5.18	<0.05
CR	22	6.4	37	8.9	1.45	—
CL	23	6.7	19	4.5	1.54	—
TER	13	3.8	28	6.7	2.98	—
TEL	13	3.8	26	6.2	1.29	—
RL	2	0.6	16	3.8	3.76	—
Total	344	100.0	418	100.0		

*—, $P > 0.05$.

TABLE VI. Association Between VACTERL and Other Anomalies in Decreasing Value of Observed/Expected (O/E) Ratios, Casuistic Derived Expected Values (N = 10,084)

	Observed	Expected	Z	P	O/E
Ambiguous genitalia	77	16.89	14.63	0.0001	4.56
Prune belly	23	5.35	7.63	0.0001	4.30
Single umbilical artery	66	17.00	11.88	0.0001	3.88
Lung hypoplasia	36	10.29	8.01	0.0001	3.50
Other intestinal defects[a]	43	16.10	6.70	0.0001	2.67
Diaphragmatic hernia	20	8.78	3.79	0.0001	2.28
Abdominal wall defect	41	26.50	2.82	0.0048	1.55
Undescended testes	40	33.00	1.22	0.222	1.21
Hydrocephaly	28	23.23	0.99	0.322	1.21
Lower limb reduction	17	14.45	0.67	0.503	1.18
Microtia	24	21.10	0.63	0.53	1.14
Arthrogryposis	18	16.06	0.48	0.63	1.12
Microphthalmia	12	12.42	−0.12	0.90	0.97
Cleft lip	53	58.41	−0.71	0.48	0.91
Talipes-Total	99	111.83	−1.21	0.23	0.89
Cephalocele	8	9.82	−0.58	0.56	0.81
Upper limb reduction	17	25.67	−1.71	0.087	0.66
High arched palate	10	16.37	−1.57	0.12	0.61
Micrognathia	37	66.51	−2.62	0.0003	0.56
Talipes-talovalgus	14	25.41	−2.26	0.02	0.55
Postaxial polydactyly	14	25.98	−2.35	0.019	0.54
Spina bifida	17	35.91	−3.16	0.0016	0.47
Syndactyly	17	40.48	−3.69	0.0002	0.42
Microcephaly	7	20.06	−2.92	0.0035	0.35
Hip dislocation	15	45.36	−4.51	0.0001	0.33
Anencephaly	5	17.25	−2.95	0.0032	0.29
Preauricular tags	13	47.75	−5.03	0.0001	0.27
Angiomas	2	21.82	−4.24	0.0002	0.09

[a]Excluding esophageal and anal atresias.

drome (14 observed/31.87 expected = 0.45; Z = −3.04; $P = 0.0024$). The latter was no longer sustained by the popular (0.79 expected; observed/expected = 17.82; Z = 14.91; $P < 0.01$), or adjusted (8.29 expected; observed/expected = 1.69; Z = 1.98; $P > 0.05$) methods. Other observed syndromes were not tested because of expected values below 5.

DISCUSSION

The Frequency of VACTERL

This work departed from a preconceived definition of VACTERL, chosen in order to produce data comparable with the two large series available in the literature: those of Khoury et al. [1983] and Czeizel and Ludanyi [1985].

The observed birth prevalence rate of VACTERL defined by at least two components was of 2.10/10,000 (524/2,493,999), which is quite similar to the 1.43/10,000 (226/1,580,000) reported by Czeizel and Ludanyi [1985], but six times lower than the 13.06 (400/306,361) reported by Khoury et al. [1983]. Such a difference cannot be entirely explained by the inclusion of other limb anomalies than upper limb reductions in the material of Khoury et al. [1983], and other differences in case ascertainment and definition may perhaps explain their higher birth prevalence rate of VACTERL. For instance, unlike the material presented here, recognized syndromes and chromosome anomalies were excluded from the material of Khoury et al. [1983], and an intermediate "mixed" category was defined between isolated and associated VACTERL cases by Czeizel and Ludanyi [1985].

The Association Among VACTERL Components

By the highly specific casuistic method [Källén, 1988], the combinations of VACTERL components taken two at a time (diads) with the highest association rates (Observed/Expected: O/E) were ATE, TEL, VA, and VTE. The five combinations involving cardiac defects (C) were included among the diads with the lowest O/E ratios. Likewise, when taken three at a time (triads), the ten combinations including C were concentrated among the lowest O/E ratios within the twenty possible triads. This suggests that the association of cardiac defects with other VACTERL components is not more frequent than with any other birth defects, thus indicating that C is not a specific component of VACTERL, so supporting Källén's [1987] original observation.

The consideration of only radial or upper limb preaxial anomalies among the limb defects seems to be a correct one in defining VACTERL association since three of the five VACTERL diads involving L had significant association rates, while none of the other limb anomaly types (other upper and lower limb reduction defects, postaxial polydactyly, syndactyly, talipes, hip dislocation, and arthrogryposis) showed association with VACTERL.

Number of Components Defining VACTERL

According to Källén and Winberg [1968], multimalformed infants (MCA patterns) should be defined by

three or more defects in order to reduce the interference of random associations when monitoring frequencies in large birth series. However, this is not the case in defining the VACTERL association, a multiple defect pattern, in which more than one (multiple defects) is conceptually different from one (single defect).

The 80% of VACTERL cases with only two component defects found in the present material (416/524 = 79.4%) is similar to those values published by Khoury et al. [1983] (324/400 = 81.0%), and Czeizel and Ludanyi [1984] (226/277 = 81.6%).

The higher frequency of cardiac defects in two-components than in three-plus VACTERL cases suggests that some cases with two components, including cardiac defects, could not belong to VACTERL. On the other hand, the lower frequency of limb defects in the former than in the latter group could indicate a high specificity of the upper limb preaxial defects as part of VACTERL, as one could speculate that the higher the number of VACTERL components, the lower the chance of overlap with other entities and the greater the chance of being VACTERL. However, these results do not seem to show any clear difference between VACTERL cases with two components and those with more than two.

Positive Association With Non-VACTERL Defects

Two of the seven non-VACTERL defects with significant ($P < 0.01$) positive association rates, single umbilical artery, and ambiguous genitalia are recognized by clinical observations to be part of VACTERL and the overlapping caudal regression complex [Duncan and Shapiro, 1990]. Another two defects, abdominal wall anomalies (mainly omphaloceles and gastroschisis) and diaphragmatic herniae are not recognized as associated with VACTERL, although omphalocele and diaphragmatic hernia show a high prevalence of associated anomalies. An epidemiologic study on abdominal wall defects in a large series of births reported a prevalence of associated anomalies (congenital heart defects, skeletal deformities, and chromosome anomalies, among others) of up to 50% for omphalocele [Baird et al., 1981]. In the present material, after excluding seven cases with omphalocele and trisomy 18, the positive association rate was no longer significant (O/E = 1.28; Z = 1.46; $P = 0.144$).

Diaphragmatic hernia, though not preferentially associated with VACTERL, is frequently part of malformation syndromes or associations. The reported prevalence of other anomalies associated with diaphragmatic hernia is variable and up to 50% [David et al., 1976; Puri et al., 1984]. Besides, diaphragmatic hernia is mainly ascertained through autopsy. In the present material, 15 of the 20 observed cases with diaphragmatic hernia had an autopsy. When these were compared with the total population of MCA infants which had autopsy (N = 1097), the O/E ratio was no longer significant (15/15.88 = 0.94; Z = 1.03; $P = 0.303$).

The remaining three non-VACTERL defects with positive association rates were prune belly, intestinal atresias (other than esophageal or anal), and lung hypoplasia. None of these are independent of VACTERL component defects. Intestinal atresias are interrelated to both esophageal and anal atresia [Spouge et al., 1986], while prune belly and lung hypoplasia could be secondary to renal or urinary tract dysfunction. All of these anomalies, as well as cardiac defects, could be considered an extension of the VATERL spectrum (C excluded, now), even when they cannot define a case as VATERL, their presence is not enough to make an associated VACTERL case out of an isolated one.

The observed higher than expected frequency of trisomy 18 syndrome in this VACTERL material is in accordance with the clinically recognized high frequency of cardiac defects in this syndrome. In the present material, 12 of the 20 observed cases with trisomy 18 had 2 VACTERL components (pairs), involving C (congenital heart disease) and thus should have been excluded as VACTERL cases, considering that congenital heart defect is not a main component of VACTERL. With the eight remaining cases, the association rate is no longer significant.

Negative Association With Non-VACTERL Defects

The lower than expected frequency of Down syndrome among VACTERL cases is not easily understood. In 13 of the 14 observed cases, the VACTERL association corresponded to a pair of components involving C (congenital heart disease). Thus, if C is removed from the definition of VATERL, only one case would have been observed having both, VACTERL association and Down syndrome, a case having renal and vertebral anomalies. One possible explanation for this apparently negative association could be that Down syndrome frequently has few major malformations. In our population of 10,084 MCA pattern infants, 82.7% of the Down syndrome cases had only one associated malformation, the most frequent being congenital heart defect (34%). If the expected values were obtained among those Down cases with more than one associated anomaly, the association would turn out to be significantly positive (Z = 3.73; $P < 0.001$). Excluding those cases with pairs of components involving C, the association rate would no longer be significant.

The only major malformations negatively associated ($P < 0.01$) with VACTERL were two neural tube defects, spina bifida, and anencephaly, while the remaining seven are low observational value defects with heterogeneous ascertainment rates. In those cases, underascertainment should not be unexpected in the presence of major malformations or neonatal death.

We believe this negative association between VACTERL and neural tube defects is an interesting fact, requiring further studies to determine the nature of its significance. It could depend on etiopathogenic mechanisms and inductive field effects which up to date are unknown for VACTERL and not fully understood for neural tube defects [Seller, 1995].

ACKNOWLEDGMENTS

This study was supported by: In the Latin American Program, the Consejo Nacional de Investigaciones Cientificas y Tecnicas (CONICET) of Argentina, the Con-

selho Nacional de Desenvolvimento Cientifico e Tecnologico (CNPq) of Brazil, and the Pan-American Health Office (PAHO).

REFERENCES

Baird PA, MacDonald EC (1981): An epidemiologic study of congenital malformations of the anterior abdominal wall in more than half a million consecutive live births. Am J Hum Genet 33:470–478.

Castilla E, Orioli I (1983): El Estudio Colaborativo Latinoamericano de Malformaciones Congenitas: ECLAMC/MONITOR. Interciencia 8:271–278.

Czeizel A, Ludanyi I (1984): VACTERL association. Acta Morphol Hung 32:75–96.

Czeizel A, Ludanyi I (1985): An aetiological study of the VACTERL association. Eur J Pediatr 144:331–337.

David TJ, Illingworth CA (1976): Diaphragmatic hernia in the southwest of England. J Med Genet 13:253–262.

Duncan PA, Shapiro LR (1993): Sirenomelia and VATER association: Possible interrelated disorders with common embryologic pathogenesis. Dysmorph Clin Genet 2:96–103.

Evans J (1982): Numerical Taxonomy in the Study of Birth Defects. In TVN Persaud (ed): "Advances in the Study of Birth Defects Series," Vol. 5: Genetic Disorders: Syndromology and Prenatal Diagnosis. New York: Alan R Liss, pp 139–160.

Källén B, Winberg J (1968): A Swedish registry of congenital malformations: Experience with continuous registration during two years with special reference to multiple malformations. Pediatrics 41:765–776.

Källén B (1987): Population surveillance of multimalformed infants: Experience with the Swedish registry of congenital malformations. Second part. J Genet Hum 35:321–338.

Källén B (1988): "Epidemiology of Human Reproduction." Boca Raton, Florida: CRC Press Inc., pp 31–35.

Kaufman RL (1973): Birth defects and oral contraceptives. Lancet i:1396.

Khoury MJ, Cordero JF, Greenberg F, James LM, Erickson JD (1983): A population study of the VACTERL association: Evidence for its etiologic heterogeneity. Pediatrics 71:815–820.

Khoury MJ, Levy WD, Erickson JD (1990): On the measurement and interpretation of birth defect associations in epidemiologic studies. Am J Med Genet 37:229–236.

Lubinsky M (1980): Female pseudohermaphroditism and associated anomalies. Am J Med Genet 6:123–136.

Lubinsky M (1986): Current Concepts: VATER and other associations: Historical perspectives and modern interpretations. Am J Med Genet Suppl 2:9–16.

Nora AH, Nora JJ (1975): A syndrome of multiple congenital anomalies associated with teratogenic exposure: The VACTERL syndrome. Arch Environ Health 30:17–21.

Puri P, Gorman F (1984): Lethal nonpulmonary anomalies associated with congenital diaphragmatic hernia: Implications for early intrauterine surgery. J Pediatr Surg 19:29–32.

Quan L, Smith D (1973): The VATER association. J Pediatr 82: 104–107.

Seller MJ (1995): Recent developments in the understanding of the etiology of neural tube defects. Clin Dysmorphol 4:93–104.

Smith DW (1982): Recognizable patterns of human malformations. In "Genetic Embryologic and Clinical Aspects," 3rd ED. Philadelphia: Saunders, pp 517–519.

Spouge D, Baird PA (1986): Imperforate anus in 700,000 consecutive liveborn infants. Am J Med Genet Suppl 2:151–161.

Temtamy S, Miller J (1974): Extending the scope of the VATER association: Definition of the VATER syndrome. J Pediatr 85:345–349.

APPENDIX A. Observed Number of Cases for Each Theoretically Possible Combination of the Six VACTERL Components

	VACTERL-isolated						VACTERL-associated					
	V	A	C	TE	R	L	V	A	C	TE	R	L
Pairs												
V	—	6	3	1	1	2	—	26	18	7	18	7
A	—	—	8	21	3	0		—	29	24	49	9
C	—	—	—	11	14	5			—	28	80	18
TE	—	—	—	—	2	4				—	11	9
R	—	—	—	—	—	1					—	1
L						—						—
Triplets												
VA	—	—	0	2	2	1	—	—	3	4	9	3
VC	—	0	—	1	1	0	—	0	—	3	3	2
VTE	—	0	0	—	0	1	—	0	0	—	0	0
VR	—	0	0	0	—	0	—	0	0	0	—	0
AC	0	—	—	0	1	1	0	—	—	3	13	1
ATE	0	—	0	—	0	2	0	—	0	—	7	3
AR	0	—	0	0	—	1	0	—	0	0	—	0
CTE	0	0	—	—	0	0	0	0	—	—	5	3
CR	0	0	—	1	—	0	0	0	—	0	—	4
TER	0	0	0	—	—	1	0	0	0	—	—	3
Quadruplets												
ACTE	0	—	—	—	—	—	1	—	—	—	—	—
ACR	1	—	—	—	—	—	1	—	—	—	—	—
ACL	0	—	—	—	—	—	0	—	—	—	—	—
ATER	0	—	—	—	—	—	3	—	—	—	—	—
ATEL	1	—	—	—	—	—	3	—	—	—	—	—
ARL	1	—	—	—	—	—	0	—	—	—	—	—
CTER	0	1	—	—	—	—	0	1	—	—	—	—
CTEL	1	0	—	—	—	—	1	0	—	—	—	—
CRL	0	0	—	—	—	—	0	1	—	—	—	—
TECR	0	0	—	—	—	—	0	0	—	—	—	—
TECL	0	0	—	—	—	—	0	0	—	—	—	—
TERL	0	0	0	—	—	—	0	1	2	—	—	—
Quintuplets												
CTERL	0	0	—	—	—	—	0	0	—	—	—	—
ATERL	1	—	—	—	—	—	0	—	—	—	—	—
ACRL	0	—	—	—	—	—	0	—	—	—	—	—
ACTEL	0	—	—	—	—	—	2	—	—	—	—	—
ACTER	0	—	—	—	—	—	1	—	—	—	—	—
Sextuplet												
ACTERL	0	—	—	—	—	—	1	—	—	—	—	—